II. REMARKS

Claims 1-72 are pending and were subject to restriction. Claims 7, 9, 14-16, 34-42, 71 and 72 have been withdrawn from consideration. Examined claims 1-6, 8, 10-13, 17-33 and 43-70 stand variously rejected under 35 U.S.C. §§ 112, first and second paragraphs, 102 and 103.

Claims 1 and 43 have been amended herein to clarify that chromosomal cellular chromatin is modified, as described throughout the specification as filed, for example on page 14, lines 22-26. In addition, claims 64 and 66 have been amended to eliminate the term "shared binding site." Entry of the foregoing amendments is respectfully requested. Applicants reserve the right to file one or more continuing applications directed to the subject matter of these claims during the pendency of this application.

Drawings

Applicants acknowledge with appreciation that the drawings submitted with the application papers have been approved by the draftsperson.

Specification

The Examiner has objected to the specification for containing an embedded hyperlink. See, Office Action, paragraph 5. Applicants have removed the embedded hyperlink by amendment herein, thereby obviating this rejection.

Double Patenting

Claims 1-72 stand provisionally rejected under 35 U.S.C. § 101 as allegedly claiming the same invention as that of claims 1-42 and 44-73 of copending application no. 10/084,826. (Office Action, paragraph 7). In addition, claims 1-6, 8, 10-13, 17-33 and 43-70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-15 and 17-20 of copending application no. 09/942,087. (Office Action, paragraph 9).

Applicants note that the provisional double patenting rejection based on co-pending application no. 10/084,826 has been obviated in view of a preliminary amendment filed in this case on April 9, 2003, canceling claims allegedly drawn to the same subject matter as claimed herein. Therefore, withdrawal of this provisional rejection is respectfully requested.

With regard to the double patenting rejection based on copending application no. 09/942,087, Applicants remind the Office that a determination of obviousness-type double patenting essentially involves the determination of obviousness under 35 U.S.C. 103, except that

the patent principally underlying the double patenting rejection is not considered prior art. *See, In re Longi,* 225 USPQ 654, 684 (Fed. Cir. 1985). Here, the pending claims are all directed to methods in which a component of a chromatin remodeling complex is used in a first molecule to modify chromatin structure, not as a transcriptional regulator. (See, *e.g.,* claim 1 and step (a) of claim 43). In fact, only claim 43 (and dependent claims therefrom) is directed to methods of modulating gene expression and, even in these claims, it is a second molecule (not the first molecule containing a component of a chromatin remodeling complex or functional fragment thereof) that acts to modulate gene expression. In contrast, the 09/942,087 application teaches methods in which a component of a chromatin remodeling complex (DMMT) is used as a transcriptional regulator of gene expression. Thus, the 09/942,087 application does not render obvious the pending claims and withdrawal of the obviousness-type double patenting rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Written Description

Claims 1-6, 8, 10-13, 17-33 and 43-70 stand rejected as allegedly containing subject matter that was not described in the specification as filed. (Office Action, paragraph 11). In particular, the specification is alleged not to adequately describe "a component" of a chromatin remodeling complex or a "functional fragment" thereof. (Office Action, paragraph 11, pages 5-6).

The written description requirement is highly fact-dependent and there is a strong presumption that an adequate written description of the claimed invention is present at the time of filing. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim,* 191 USPQ 90 (CCPA 1976). The first step in a written description inquiry is to properly construe the claims as issue:

> Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. [citation omitted] The entire claim must be considered, including the preamble and the transitional phrase. The claims as a whole, including all the limitations found in the preamble, the transitional phrase, and the body of the claims, must be sufficiently supported to satisfy the written description requirement. (66 Fed. Reg. 1099, 1105).

Only after the claims are properly constructed, can an analysis of the adequacy of the description begin. Furthermore, the written description requirement of section 112 does not require that the claims be limited in scope to particular sequences (*e.g.,* particular chromatin

remodeling complexes). Indeed, the courts have consistently found that macromolecule such as DNA and proteins may be properly defined by one or more of the following parameters: "structure, formula, chemical name or physical properties." *Fiers v. Revel*, 25 USPQ2d 1601 (Fed. Cir. 1993). The recent PTO guidelines on written description are equally clear that particular sequences are not required to satisfy 35 U.S.C. § 112, first paragraph:

> [t]he description need only describe in detail that which is new or not conventional. This is equally true whether the claimed invention is a product or a process. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such characteristics. (Final Examiner Guidelines on Written Description, 66 Fed. Reg. 1099, emphasis added).

Simply put, there is absolutely no requirement that Applicants disclose any particular polypeptide sequences making up the claimed components of chromatin remodeling complexes. Rather, the test is whether the specification reasonably conveys possession of the claimed subject matter in view of a thorough reading of the disclosure and the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to publications available to the public prior to the filing date of the application. *See, e.g., In re Lukach,* 169 USPQ 795, 796 (CCPA 1971). *In re Lange,* 209 USPQ 288 (CCPA 1981).

Applying these rules to the instant application, Applicants submit that the specification more than adequately describes the subject matter of pending claims 1-6, 8, 10-13, 17-33 and 43-70.

First and foremost, these claims do not, as asserted by the Office, encompass chromatin remodeling complexes that "may be nothing more than a hydrogen ion..." (Office Action, paragraph 11). Rather, when properly construed, it is clear that the pending claims all require that the methods involve a fusion molecule that includes a polypeptide component of a chromatin remodeling complex or a functional fragment thereof. The term "component of a chromatin remodeling complex" is clearly described, for example, at page 23, line 24 through page 25, line 22; and numerous specific examples of chromatin remodeling complexes and their components are provided beginning at page 25 and continuing through page 34. The specification more than adequately describes both relevant, identifying structural (*e.g.,* the structure and sequence of numerous exemplary components of chromatin remodeling complexes) and functional (*e.g.,*

modifies chromatin structure, ATPase activity) characteristics of the claimed "components" of chromatin remodeling complexes useful in the claimed methods. A myriad of representative examples of components of chromatin remodeling complexes are described, in detail, on page 23, line 23 through page 34, line 28. What was not known prior to Applicants' disclosure is that these proteins or fragments thereof could be used as claimed. The specification more than adequately describes a large number of chromatin remodeling complexes, their component polypeptides, and how to select known components of chromatin remodeling complexes and use these components in the claimed methods. Therefore, the specification adequately describes sufficient, relevant structural and functional features of the polypeptides used for the claimed methods.

Furthermore, with regard to the term "functional fragment," Applicants direct the Examiner's attention to page 20, starting on line 21:

> A functional fragment of a protein, polypeptide or nucleic acid is a protein, polypeptide or nucleic acid whose sequence is not identical to the full-length protein, polypeptide or nucleic acid, yet retains the same function as the full-length protein, polypeptide or nucleic acid. A functional fragment can possess more, fewer, or the same number of residues as the corresponding native molecule, and/or can contain one ore [sic] more amino acid or nucleotide substitutions. Methods for determining the function of a nucleic acid (*e.g.*, coding function, ability to hybridize to another nucleic acid) are well-known in the art. Similarly, methods for determining protein function are well-known. For example, the DNA-binding function of a polypeptide can be determined, for example, by filter-binding, electrophoretic mobility-shift, or immunoprecipitation assays. See Ausubel *et al., supra*. The ability of a protein to interact with another protein can be determined, for example, by co-immunoprecipitation, two-hybrid assays or complementation, both genetic and biochemical. See, for example, Fields *et al.* (1989) *Nature* **340:**245-246; U.S. Patent No. 5,585,245 and PCT WO 98/44350.

In view of the foregoing, it is clear that one of skill in the art would understand that Applicants were in possession of the claimed "functional fragments" at the time of filing.

In sum, ample structure (*e.g.,* organization, order, components) and identifying characteristics of the claimed methods are provided so that a skilled artisan would recognize that Applicants were in possession of the claimed invention at the time of filing. As such, the written description requirement is satisfied and Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-6, 8, 10-13, 17-33 and 43-70 stand rejected as allegedly indefinite. (Office Action, paragraphs 14-16). In particular, the metes and bounds of the terms "component," "binds to a shared binding site," and "modifying" are allegedly not known.

Applicants traverse the rejections and supporting remarks.

It is axiomatic that definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular disclosure at issue, (2) the teachings of the art, and (3) the interpretation that would be given by one possessing an ordinary level of skill in the pertinent art the time the invention was made. *See, e.g., In re Marosi,* 218 USPQ 289 (Fed. Cir. 1983). Consequently, a claim that is understandable to one of skill in the art meets the requirements of the second paragraph of 35 U.S.C. § 112.

With this legal framework in mind, Applicants note the claims would have been clear to the skilled artisan in view of the specification as filed.

With regard to the term "component," Applicants note again that is clearly defined on pages 23-35 of the specification. In particular, Applicants direct the Examiner's attention to page 23, line 24 through page 24, line 2, where the term is initially defined:

> Two major types of chromatin modification have been described. The first is dependent on covalent modification. Covalent modification of histones occurs by processes such as, for example, acetylation and deacetylation. Covalent modification of DNA is exemplified by methylation of cytosine residues in CpG dinucleotides. The second type of modification results in changes in nucleosome location and/or conformation, and relies on the activity of ATP-driven chromatin remodeling machines. Both types of chromatin modification are carried out *in vivo* by multiprotein complexes. For the purposes of the present disclosure, proteins involved in either of these types of chromatin modification can comprise a component of a chromatin-remodeling complex.

Twelve more pages describing exemplary chromatin remodeling complexes and their components follow this initial definition. Thus, the metes and bounds of the term "component" of a chromatin remodeling complex would be clear to the skilled artisan when read in light of the specification and in view of the state of the art at the time of filing.

Similarly, Applicants submit that the term "shared binding site," is sufficiently definite in view of the specification as a whole. Nonetheless, to expedite prosecution, this term has been

removed by amendment herein, thereby obviating the rejections set forth in paragraph 15 of the Office Action.

Claims 1 and 43 have been amended to address the rejection set forth in paragraph 16 of the Office Action.

In view of the foregoing remarks and amendments, Applicants request that the rejections be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 1-6, 8, 10, 12, 13, 17-20, 43-47, 55-57, 59-62, 64-66 and 68-70 stand rejected under 102(e) as allegedly anticipated by US 2002/0045158A1 (hereinafter "Case"). (Office Action, paragraph 18). In addition, claims 1-6, 8, 12, 13, 17, 43-46, 55, 57, 59-61 and 64-70 stand rejected under 102(e) as allegedly anticipated by US 2002/0188103A1 (hereinafter "Bestor"). (Office Action, paragraph 19). Applicants address each rejection in turn.

With regard to Case, Applicants note that this reference cannot be used as a 102(e) reference for its teachings regarding chromatin remodeling complexes. The disclosure regarding chromatin-remodeling complexes was not introduced into Case until February 8, 2001, fully half a year **after** Applicants' latest effective priority date of August 28, 2000. Thus, Case is not a proper 102(e) reference against the pending claims.

Turning to Bestor, Applicants note that the pending claims are all directed to methods in which chromosomal chromatin is modified. In contrast, Bestor is totally silent with respect to chromatin structure, let alone *modification* of chromatin structure. Bestor describes and demonstrates modulation of transcription and viral replication, processes that are totally unrelated to the claimed methods for modification of chromatin structure. Moreover, the transcriptional modulation and viral replication effects disclosed by Bestor occur only on plasmid or viral genomes; *not* in chromosomal chromatin, as claimed. Thus, Bestor fails entirely to describe or suggest methods for modification of any type of chromatin at all, let alone chromosomal chromatin, as claimed by Applicants.

In sum, because Case is not a reference against the pending claims and because Bestor does not describe, demonstrate or suggest the methods as claimed, the references do not anticipate the pending claims and withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1-6, 8, 10, 12, 13, 17-33, and 43-70 stand rejected under 103(a) as allegedly obvious over Case and Bestor in view of U.S. Patent No. 6,015,709 (hereinafter "Natesan") and

U.S. Patent No. 6, 153,383 (hereinafter "Verdine"). (Office Action, paragraph 21). Case and Bestor are cited as above. Natesan and Verdine are cited for allegedly teaching a fusion protein with a DNA binding domain linked to a transcriptional regulatory domain that modifies a chromatin region. (Office Action, paragraph 21).

For the reasons detailed above, the primary references (Case and Bestor) do not teach or suggest the methods as claimed. In particular, Case cannot be used as a reference against the pending claims while Bestor fails entirely to teach or suggest the modification of chromosomal chromatin.

The secondary references fail to supply what is missing from the primary references. Natesan is silent as to chromatin remodeling complexes entirely. For its part, Verdine describes chimeric proteins that necessarily include a ligand-binding domain. Nowhere does this reference suggest that the ligand-binding domain should be a component of a chromatin-remodeling complex, as claimed.

Therefore, there is no combination of the cited references that would reasonably lead one of skill in the art to the claimed subject matter and Applicants respectfully request that the rejection be withdrawn.

III. CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

Date: April 11, 2003

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Version Showing Changes Made

In the specification:

The paragraph beginning on line 12 of page 15 has been amended as follows:

-- Target sites for various transcription factors are known. *See*, for example, Wingender *et al.* (1997) *Nucleic Acids Res.* **25**:265-268 and the TRANSFAC Transcription Factor database [at http://transfac.gbf.de/TRANSFAC/] available on the internet, accessed on April 13, 2000. In general, target sites for newly-discovered transcription factors, as well as other types of exogenous molecule, can be determined by methods that are well-known to those of skill in the art such as, for example, electrophoretic mobility shift assay, exonuclease protection, DNase footprinting, chemical footprinting and/or direct nucleotide sequence determination of a binding site. See, for example, Ausubel *et al., supra*, Chapter 12.--

In the claims:

The claims have been amended as follows:

1. (Amended) A method for modifying a region of interest in chromosomal cellular chromatin, the method comprising the step of contacting the chromosomal cellular chromatin with a fusion molecule that binds to a binding site in the region of interest, wherein the fusion molecule comprises a DNA binding domain and a component of a chromatin remodeling complex or functional fragment thereof, and further wherein the contacting is conducted under conditions such that the component of the chromatin remodeling complex or functional fragment thereof modifies the chromosomal cellular chromatin in [thereby modifying] the region of interest.

43. (Amended) A method for modulating expression of a gene, the method comprising the steps of:

a) contacting chromosomal cellular chromatin with a first fusion molecule that binds to a binding site in the chromosomal cellular chromatin, wherein the binding site is in the gene and wherein the first fusion molecule comprises a DNA-binding domain and a component of a chromatin remodeling complex or functional fragment thereof and further wherein the contacting is conducted under conditions such that the component of the chromatin remodeling complex or

functional fragment thereof modifies the chromosomal cellular chromatin; and

b) further contacting the cellular chromatin with a second molecule that binds to a target site in the gene and modulates expression of the gene.

64. (Amended) The method of claim 59 wherein the first fusion molecule binds to [a shared binding site in] two or more of the plurality of genes.

66. (Amended) The method of claim 59 wherein the second molecule binds to a [shared target site in] two or more of the plurality of genes.

Currently Pending Claims

1. (Amended) A method for modifying a region of interest in chromosomal cellular chromatin, the method comprising the step of contacting the chromosomal cellular chromatin with a fusion molecule that binds to a binding site in the region of interest, wherein the fusion molecule comprises a DNA binding domain and a component of a chromatin remodeling complex or functional fragment thereof, and further wherein the contacting is conducted under conditions such that the component of the chromatin remodeling complex or functional fragment thereof modifies the chromosomal chromatin in the region of interest.

2. The method of claim 1, wherein the cellular chromatin is present in a plant cell.

3. The method of claim 1, wherein the cellular chromatin is present in an animal cell.

4. The method of claim 3, wherein the cell is a human cell.

5. The method of claim 1, wherein the fusion molecule is a fusion polypeptide.

6. The method of claim 1, wherein the DNA-binding domain comprises a zinc finger DNA-binding domain.

7. *Withdrawn*

8. (Amended) The method of claim 1, wherein the component of a chromatin remodeling complex or functional fragment thereof is an enzymatic component.

9. *Withdrawn*

10. The method of claim 1, wherein chromatin modification facilitates detection of a sequence of interest.

11. The method of claim 10, wherein the sequence of interest comprises a single

nucleotide polymorphism.

12. The method of claim 1, wherein chromatin modification facilitates activation of a gene of interest.

13. The method of claim 1, wherein chromatin modification facilitates repression of a gene of interest.

14 to 16. *Withdrawn*

17. The method of claim 1, wherein the region of interest comprises a gene.

18. The method of claim 17, wherein the gene encodes a product selected from the group consisting of vascular endothelial growth factor, erythropoietin, androgen receptor, PPAR-γ2, p16, p53, pRb, dystrophin and e-cadherin.

19. The method of claim 1, further comprising the step of contacting the cellular chromatin with a second molecule.

20. The method of claim 19, wherein the second molecule is a transcriptional regulatory protein.

21. The method of claim 19, wherein the second molecule is a fusion molecule.

22. The method of claim 21, wherein the second molecule is a fusion polypeptide.

23. The method of claim 21, wherein the second molecule comprises a zinc finger DNA-binding domain.

24. The method of claim 23, wherein the second molecule further comprises a transcriptional activation domain.

25. The method of claim 23, wherein the second molecule further comprises a transcriptional repression domain.

26. The method of claim 23, wherein the second molecule further comprises a polypeptide sequence selected from the group consisting of a histone acetyl transferase, a histone deacetylase, a functional fragment of a histone acetyl transferase, and a functional fragment of a histone deacetylase.

27. The method of claim 19, further comprising the step of contacting the cellular chromatin with a third molecule.

28. The method of claim 27, wherein the third molecule is a transcriptional regulatory protein.

29. The method of claim 27,wherein the third molecule is a fusion molecule.

30. The method of claim 29,wherein the third molecule is a fusion polypeptide.

31. The method of claim 29, wherein the third molecule comprises a zinc finger DNA-binding domain.

32. The method of claim 31, wherein the third molecule further comprises a transcriptional activation domain.

33. The method of claim 31, wherein the third molecule further comprises a transcriptional repression domain.

34. to 42. *Withdrawn*

43. (Amended) A method for modulating expression of a gene, the method comprising the steps of:

a) contacting chromosomal cellular chromatin with a first fusion molecule that binds to a binding site in the chromosomal cellular chromatin, wherein the binding site is in the gene and wherein the first fusion molecule comprises a DNA-binding domain and a component of a chromatin remodeling complex or functional fragment thereof and further wherein the contacting is conducted under conditions such that the component of the chromatin remodeling complex or

functional fragment thereof modifies the chromosomal cellular chromatin; and

b) further contacting the cellular chromatin with a second molecule that binds to a target site in the gene and modulates expression of the gene.

44. The method of claim 43, wherein modulation comprises activation of expression of the gene.

45. The method of claim 43, wherein modulation comprises repression of expression of the gene.

46. The method of claim 43 wherein the DNA-binding domain of the first fusion molecule comprises a zinc finger DNA-binding domain.

47. The method of claim 43 wherein the second molecule is a polypeptide.

48. The method of claim 47 wherein the second molecule comprises a zinc finger DNA-binding domain.

49. The method of claim 48, wherein the second molecule further comprises an activation domain.

50. The method of claim 48, wherein the second molecule further comprises a repression domain.

51. The method of claim 43 wherein the second molecule is a transcription factor.

52. The method of claim 51 wherein the transcription factor is an exogenous molecule.

53. The method of claim 51 wherein the transcription factor is an endogenous molecule.

54. The method of claim 43 wherein the first fusion molecule and the second molecule each comprise a zinc finger DNA-binding domain.

55. The method of claim 43 wherein a plurality of first fusion molecules is contacted with cellular chromatin, wherein each of the first fusion molecules binds to a distinct binding site.

56. The method of claim 43, wherein a plurality of second molecules is contacted with cellular chromatin, wherein each of the second molecules binds to a distinct target site.

57. The method of claim 55 wherein at least one of the first fusion molecules comprises a zinc finger DNA-binding domain.

58. The method of claim 56 wherein at least one of the second molecules comprises a zinc finger DNA-binding domain.

59. The method of claim 43 wherein the expression of a plurality of genes is modulated.

60. The method of claim 59 wherein a plurality of first fusion molecules is contacted with cellular chromatin, wherein each of the first fusion molecules binds to a distinct binding site.

61. The method of claim 60 wherein at least one of the first fusion molecules is a zinc finger fusion polypeptide.

62. The method of claim 59, wherein a plurality of second molecules is contacted with cellular chromatin, wherein each of the second molecules binds to a distinct binding site.

63. The method of claim 62 wherein at least one of the second molecules is a zinc finger fusion polypeptide.

64. (Amended) The method of claim 59 wherein the first fusion molecule binds to two or more of the plurality of genes.

65. The method of claim 64 wherein the first fusion molecule is a zinc finger fusion

polypeptide.

66. (Amended) The method of claim 59 wherein the second molecule binds two or more of the plurality of genes.

67. The method of claim 66 wherein the second molecule is a zinc finger fusion polypeptide.

68. The method of claim 1, wherein chromatin modification results in the generation of an accessible region in the cellular chromatin.

69. The method of claim 68, wherein generation of the accessible region facilitates binding of an exogenous molecule.

70. The method of claim 69, wherein the exogenous molecule is selected from the group consisting of polypeptides, nucleic acids, small molecule therapeutics, minor groove binders, major groove binders and intercalators.

71. and 72. *Withdrawn*